

- a multiple cloning site; and
- (b) transforming an appropriate yeast strain with the vector of step (a) and maintaining the yeast strain under suitable conditions for the production of the anti-angiogenic restin protein, or the mutant, derivative, fragment or fusion protein thereof;

thereby producing a biologically active anti-angiogenic restin protein, or mutant, derivative, fragment or fusion protein thereof.

6. (Amended) The method of Claim 1 wherein the restin protein, mutant, derivative, fragment or fusion protein is produced at a concentration of 10-20 milligrams or more per liter of culture fluid.

8. (Amended) The method of Claim 1 wherein the isolated polynucleotide of step (a) additionally comprises a polynucleotide linker and the anti-angiogenic restin protein, mutant, derivative, fragment or fusion protein thereof produced in step (b) additionally comprises at least one amino acid residue resulting from the polynucleotide linker.

9. (Amended) The method of Claim 8 wherein the anti-angiogenic restin protein, mutant, derivative, fragment or fusion protein produced comprises two additional amino-terminus amino acid residues.

14. (Amended) The method of Claim 1 wherein the vector of step (a) comprises a pPICZαA plasmid wherein the plasmid contains a multiple cloning site, said cloning site comprising a His.Tag motif and wherein the anti-angiogenic restin protein, mutant, derivative, fragment or fusion protein thereof produced in step (b) comprises a histidine tag motif.

17. (Amended) The method of Claim 14 wherein the restin protein, mutant, derivative, fragment or fusion protein is produced at a concentration of 10-20 milligrams or more per liter of culture fluid.

22. (Amended) A method of producing a biologically active anti-angiogenic restin protein, or a biologically active mutant, fragment, derivative or fusion protein thereof, comprising:
- (a) inserting an isolated polynucleotide comprising a polynucleotide sequence encoding an anti-angiogenic restin protein, or a mutant, derivative, fragment or fusion protein thereof, wherein the polynucleotide additionally comprises a linker, wherein the polynucleotide linker encodes at least one amino acid, into a yeast expression vector comprising a pPICz $\alpha$ A plasmid wherein the plasmid contains a multiple cloning site; and
  - (b) transforming a *Pichia pastoris* yeast strain with the vector of step (a) and maintaining the yeast strain under suitable conditions for the production of the anti-angiogenic restin protein comprising at least one amino acid residue resulting from the linker polynucleotide;
- thereby producing a biologically active anti-angiogenic restin protein, or a mutant, derivative, fragment or fusion protein thereof.

23. (Amended) The method of Claim 22 wherein the polynucleotide additionally encodes angiostatin, endostatin, or mutants, derivatives, fragments or fusion proteins thereof, or any combination thereof.

25. (Amended) A method of producing a biologically active anti-angiogenic restin protein, or a biologically active mutant, fragment, derivative or fusion protein thereof, comprising:
- (a) inserting an isolated polynucleotide comprising a polynucleotide sequence encoding an anti-angiogenic restin protein, or a mutant, derivative, fragment or fusion protein thereof, wherein the polynucleotide additionally comprises a linker, wherein the polynucleotide linker encodes at least one amino acid, into a yeast expression vector comprising a pPICz $\alpha$ A plasmid wherein the plasmid contains a multiple cloning site and wherein the cloning site additionally comprises a